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A defect in harmonin, a PDZ domain-containing protein expressed in the inner ear sensory hair cells, underlies Usher syndrome type 1C.

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Usher syndrome type 1 (USH1) is an autosomal recessive sensory defect involving congenital profound sensorineural deafness, vestibular dysfunction and blindness (due to progressive retinitis pigmentosa)1. Six different USH1 loci have been reported. So far, only MYO7A (USH1B), encoding myosin VIIA, has been identified as a gene whose mutation causes the disease. Here, we report a gene underlying USH1C (MIM 276904), a USH1 subtype described in a population of Acadian descendants from Louisiana and in a Lebanese family. We identified this gene (USH1C), encoding a PDZ-domain-containing protein, harmonin, in a subtracted mouse cDNA library derived from inner ear sensory areas. In patients we found a splice-site mutation, a frameshift mutation and the expansion of an intronic variable number of tandem repeat (VNTR). We showed that, in the mouse inner ear, only the sensory hair cells express harmonin. The inner ear Ush1c transcripts predicted several harmonin isoforms, some containing an additional coiled-coil domain and a proline- and serine-rich region. As several of these transcripts were absent from the eye, we propose that USH1C also underlies the DFNB18 form of isolated deafness.

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